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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/612,179	07/02/2003	Roland Kreutzer	26421-15777 US	5239

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EXAMINER	
CHONG, KIMBERLY	

ART UNIT	PAPER NUMBER
1635	

NOTIFICATION DATE	DELIVERY MODE
10/20/2010	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	10/612,179	KREUTZER ET AL.	
	Examiner	Art Unit	
	KIMBERLY CHONG	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *19 April 2010*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *16-29* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *16-29* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *05/25/2010*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of Application/Amendment/Claims

Applicant's response filed 04/19/2010 has been considered. Rejections and/or objections not reiterated from the previous office action mailed 12/17/2009 are hereby withdrawn. The following rejections and/or objections are either newly applied or are reiterated and are the only rejections and/or objections presently applied to the instant application. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

With entry of the amendment filed on 04/19/2010 claims 16-29 are pending in the application.

Information Disclosure Statement

The submission of the Information Disclosure Statement on 05/25/2010 is in compliance with 37 CFR 1.97. The information disclosure statement has been considered by the examiner and signed copies have been placed in the file.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 16-29 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter

which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a new matter rejection.

Claims 16-29 are drawn to a dsRNA of 21 base pairs wherein degradation of an RNA transcript is by "dsRNA-mediated interference". Claim 29 requires the limitation wherein the dsRNA-mediated interference occurs due to enzymes induced by the dsRNA.

These claims contain subject matter that was not described in the specification or even contemplated by the instant specification. Applicant points to page 3, lines 17-25 for support for the limitation "wherein degradation of an RNA transcript is by "dsRNA-mediated interference". This pinpoint of the specification is reproduced below in bold type along with the entire paragraph. It is clear that where Applicant points to support is taken out of context.

"[0011] In particular, dsRNA with a length of over 50 nucleotide pairs induces certain cellular mechanisms, for example the dsRNA-dependent protein kinase or the 2-5A system, in mammalian and human cells. This leads to the disappearance of the **interference effect mediated by the dsRNA** which exhibits a defined sequence. As a consequence, protein biosynthesis in the cell is blocked. The present invention overcomes this disadvantage in particular."

The paragraph discusses dsRNA over 50 nucleotide base pairs inducing protein kinase mechanisms in cells which "leads to the disappearance of the interference effect mediated by the dsRNA." This paragraph does not provide support for a method of inhibiting expression of a target gene using a dsRNA 21 nucleotides in length wherein the degradation is mediated by dsRNA interference. The claimed dsRNA of 21 nucleotides in length being capable of inhibiting gene expression in a mammalian cell

via dsRNA interference is not referenced anywhere else in the specification nor does Applicant point to support for this limitation anywhere else in the instant specification.

Applicant further points to support for the limitation "wherein the dsRNA-mediated interference occurs due to enzymes induced by the dsRNA" at page 2, lines 11-21. This pinpoint of the specification is reproduced below in bold type along with the entire paragraph.

> "[0005] It is known from Fire, A. et al., NATURE, Vol. 391, pp. 806 that dsRNA whose one strand is complementary in segments to a nematode gene to be inhibited inhibits the, expression of this gene highly efficiently. **It is believed that the particular activity of the dsRNA used in nematode cells is not due to the antisense principle but possibly on catalytic properties of the dsRNA, or enzymes induced by it.** Nothing is mentioned in this paper on the activity of specific dsRNA with regard to inhibiting the gene expression, in particular in mammalian and human cells."

This paragraph discusses the work of Fire et al. who uses longer dsRNA to inhibit gene expression in nematodes wherein Applicants conclude what was thought of as the possible mechanism of this phenomenon using dsRNA. A complete reading of the paragraph concludes with " [n]othing is mentioned in this paper on the activity of specific dsRNA with regard to inhibiting the gene expression...". Thus it is clear from this paragraph that Applicant was merely reciting the work of others and the thoughts on the mechanisms of action of this new phenomenon of gene silencing. This paragraph does not provide support for a method of inhibiting expression of a target gene using a dsRNA 21 nucleotides in length wherein the dsRNA-mediated interference occurs due to enzymes induced by the dsRNA. The claimed dsRNA of 21 nucleotides in length being capable of inhibiting gene expression in a mammalian cell wherein the dsRNA-mediated interference occurs due to enzymes induced by the dsRNA is not recited

anywhere else in the specification nor does Applicant point to support for this application in any other place in the instant specification.

If Applicant believes that such support is present in the specification and claimed priority documents, Applicant should point, with particularity using page and line, to where such support is to be found.

Therefore, for purposes of applying prior art, the effective filing date is 07/02/2003, which is the filing date of the instant application.

New Claim Rejections

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422

F.2d 438, 164 USPQ 619 (CCPA 1970); and In *re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 16-29 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 4, 7, 9, 11, 13-17, 19 and 21 of copending Application No. 11/982,425. Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims of each application are directed to a dsRNA of 21 nucleotides wherein the strands are further linked by a disulfide bridge. These instant claims are an obvious variation of the '425 claims because it would have been obvious to use the dsRNA in methods of inhibiting gene expression in mammalian cells in vivo to treat conditions associated with aberrant expression from target genes.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claims 16-29 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 2, 5, 7, 9, and 11-17 of copending Application No. 11/982,345. Although the conflicting claims are not identical, they are not patentably distinct from each other because the instant application is directed to a dsRNA of 21 nucleotides wherein the strands are linked by a disulfide bridge. These claims are an obvious variation of the '345 claims because it would have been obvious to use the instant dsRNA in methods of inhibiting gene expression in mammalian cells in vivo to treat conditions associated with aberrant expression from target genes.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claims 16-29 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 2-9 of copending Application No. 11/982,434. Although the conflicting claims are not identical, they are not patentably distinct from each other because the instant application is directed to a dsRNA of 21 nucleotides wherein the strands are linked by a disulfide bridge. These claims not patentably distinct over the claims of the '434 application drawn to a method of inhibiting expression in mammalian cells with a dsRNA of 21 nucleotides wherein the strands are linked by a disulfide bridge.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claims 16-29 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 4, 7, 9, 11, 13-16, 18 and 19 of copending Application No. 11/982,441. Although the conflicting claims are not identical, they are not patentably distinct from each other because each of the applications are directed to a dsRNA of 21 nucleotides wherein the strands are further linked by a disulfide bridge. The claims are not patentably distinct from each other.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claims 16-29 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over 26, 29, 30, 32, 33, 35 and 56-59 of copending Application No. 10/382,395. Although the conflicting claims are not identical, they are not patentably distinct from each other because the instant application is directed to a dsRNA of 21 nucleotides wherein the strands are linked by a disulfide bridge. These claims not patentably distinct over the claims of the '395 application drawn to a method of inhibiting expression in mammalian cells with a dsRNA of 21 nucleotides wherein the strands are further chemically linked because it would have been obvious to use the instant dsRNA in the methods of '395.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claims 16-29 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 4, 7, 9, 11, 13-16, 18 and 19 of copending Application No. 11/982,305. Although the conflicting claims are not identical, they are not patentably distinct from each other because the instant application is directed to a dsRNA of 21 nucleotides wherein the strands are further linked by a disulfide bridge. It would have been obvious to make a medicament comprising a dsRNA of 21 nucleotides in length of the '305 application wherein the strands are further chemically linked for methods of using to inhibit gene expression in a cell.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 16-29 are rejected under 35 U.S.C. 103(a) as being unpatentable over Tuschl et al. (WO 02/44321, cited on IDS), Bernstein et al. (Nature 2001) and Gao et al. (Nucleic Acids Research 1995).

The claims are directed to a dsRNA that is 21 nucleotides in length wherein the separate strands are chemically linked with a disulfide bridge, wherein the degradation of an RNA transcript is by dsRNA-mediated interference, wherein the dsRNA mediated interference occurs due to enzymes induced by the dsRNA.

Tuschl et al. teach a dsRNA that is 21-23 nucleotides in length wherein the dsRNA inhibits the expression of a target gene (see Examples). Tuschl et al. teach the inhibition is by RNAi, the dsRNA can be fully complementary to the target gene, can comprise modified nucleotides and formed by two separate strands (see page 2-9). Tuschl et al. does not specifically teach strands can be chemically linked, the linker comprises a C18 linker group, the RNA transcript is a primary or processed RNA transcript, or teach the dsRNA mediated interference occurs dues to enzymes induced by the dsRNA.

At the time the invention was made, those of ordinary skill in the art were aware that formation of a chemical linkage provides stabilization to a duplex structure. See, for example, Gao et al., who teach the use of aliphatic linkers with terminal thiol groups. When incorporated into complementary oligonucleotides which are allowed to hybridize, these thiols oxidize to form disulfides. Gao et al. further teach the incorporation of triethylene glycol groups as a replacement of a hairpin loop. Gao et al. teach that the

introduction of both disulfide bridges and ethylene glycol groups increase the thermal stability of the duplex.

Also at the time the invention was made, it was known that RNAi is a mechanism through which dsRNAs silence genes and that the guide strand of a dsRNA is incorporated into a RISC enzyme that targets mRNAs for degradation (see Bernstein et al., at least page 365). Thus the activation of an enzyme induced by a dsRNA is an inherent property of dsRNA-mediated interference.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to make a dsRNA wherein a non-nucleotide linker joins these two complementary regions. One of ordinary skill in the art would find it obvious to make the dsRNA of Tuschl et al. wherein a linker that forms a disulfide bridge is incorporated to increase the stability of the two strands. One of ordinary skill would have reason to do so because as demonstrated by Gao et al. these non-nucleotide linkers provide stabilization to duplexes containing them. It would have further been obvious to target a primary or processed RNA transcript as Tuschl et al. teach this phenomenon of RNAi is an efficient way to target specific genes for silencing of gene expression.

One would expect reasonable success at incorporating a chemical linker between the two strands of the dsRNA as this was taught by Gao et al. and further one would have expected to be able to make a dsRNA targeted to a primary or processed RNA transcript as Tuschl et al. teach how to make and use a dsRNA to target any desired gene associated with any type of conditions.

Thus, the invention of 16-29 would have been obvious, as a whole, at the time the invention was made.

Claims 16-29 are rejected under 35 U.S.C. 103(a) as being unpatentable over Agrawal et al. (WO 94/01550, cited on IDS), Baracchini et al. (US 5,801,154), Bennett et al. (US 5,703,054), and Gao et al. (Nucleic Acids Research 1995).

The claims are directed to a dsRNA that is 21 nucleotides in length wherein the separate strands are chemically linked with a disulfide bridge, wherein the degradation of an RNA transcript is by dsRNA-mediated interference, wherein the dsRNA mediated interference occurs due to enzymes induced by the dsRNA.

Agrawal et al. teach self-stabilized oligonucleotides comprising a target hybridizing region and a self-complementary region. On page 15 Agrawal et al. teach that the self-complementary region of the oligonucleotide is fully or partially complementary to the hybridizing region while at page 9, line 30 through page 10 line 1 it is taught that the target hybridizing region is complementary to a nucleic acid sequence from a variety of sources including viruses, pathogens, cellular genes or gene transcripts and is about 8 to about 50 nucleotides in length. On page 8 Agrawal et al. teach that the self-stabilized oligonucleotide is composed of ribonucleotides, deoxynucleotides and/or modified nucleotides. Page 15 and 16 describe embodiments where the oligonucleotide is a single nucleic acid strand that forms a double stranded structure as well as an embodiment where the self-complementary region is connected

to the hybridizing region by a non-nucleotide linker that is preferably a polyethylene glycol linker. Use of a non-nucleotide linker would make the self-complementary region and the hybridizing region two separate complementary nucleic acid strands. On pages 17, line 27 through page 18 Agrawal et al. teach that the self-stabilized oligonucleotides can be administered to the cells of an animal to inhibit gene expression in the animals. In the working examples Agrawal et al. use sequences of 20 and 25 nucleotides but do not specifically exemplify an embodiment wherein the individual strands are 21 nucleotides in length.

Applicant argues that Agrawal do not teach two separate RNA single strands that are chemically linked as claimed and do not teach a dsRNA that is not autocomplemenary. To the contrary, the use of a non-nucleotide linker would make the self-complementary region and the hybridizing region two separate complementary nucleic acid strands and this would meet the limitations of the instant claims. (see page 15, starting at line 31).

On pages 17, line 27 through page 18 Agrawal et al. teach that the self-stabilized oligonucleotides can be administered to the cells of an animal to inhibit gene expression in the animals. In the working examples Agrawal et al. use sequences of 20 and 25 nucleotides but do not specifically exemplify an embodiment wherein the individual strands are 21 nucleotides in length.

Agrawal et al. do not specifically teach the dsRNA inhibits expression using dsRNA-mediated interference or that the interference occurs via an enzyme induced by the dsRNA. Because the dsRNA is substantially identical to the claimed dsRNA, the

dsRNA inherently posses the functional characteristics of the claimed dsRNA, namely inhibitions of expression of a mammalian target using dsRNA-mediated interference wherein the interference occurs via an enzyme induced by the dsRNA.

The MPEP states:

A REFERENCE TEACHING PRODUCT APPEARING TO BE SUBSTANTIALLY IDENTICAL IS MADE THE BASIS OF A REJECTION, AND THE EXAMINER PRESENTS EVIDENCE OR REASONING TENDING TO SHOW INHERENCY, THE BURDEN SHIFTS TO THE APPLICANT TO SHOW AN UNOBVIOUS DIFFERENCE

"[T]he PTO can require an applicant to prove that the prior art products do not necessarily or inherently possess the characteristics of his [or her] claimed product. Whether the rejection is based on inherency' under 35 U.S.C. 102, on prima facie obviousness' under 35 U.S.C. 103, jointly or alternatively, the burden of proof is the same...[footnote omitted]." The burden of proof is similar to that required with respect to product-by-process claims. *In re Fitzgerald,* 619 F.2d 67, 70, 205 USPQ 594, 596 (CCPA 1980) (quoting *In re Best,* 562 F.2d 1252, 1255, 195 USPQ 430, 433-34 (CCPA 1977)).

MPEP 2112.01:

PRODUCT AND APPARATUS CLAIMS WHEN THE STRUCTURE RECITED IN THE REFERENCE IS SUBSTANTIALLY IDENTICAL TO THAT OF THE CLAIMS, CLAIMED PROPERTIES OR FUNCTIONS ARE PRESUMED TO BE INHERENT

Where the claimed and prior art products are identical or substantially identical in structure or composition, or are produced by identical or substantially identical processes, a prima facie case of either anticipation or obviousness has been established. In re Best, 562 F.2d 1252, 1255, 195 USPQ 430, 433 (CCPA 1977). When the PTO shows a sound basis for believing that the products of the applicant and the prior art are the same, the applicant has the burden of showing that they are not. *In re Spada*, 911 F.2d 705, 709, 15 USPQ2d 1655, 1658 (Fed. Cir. 1990). Therefore, the prima facie case can be rebutted by evidence showing that the prior art products do not necessarily possess the characteristics of the claimed product. *In re Best*, 562 F.2d at 1255, 195 USPQ at 433.

A REJECTION UNDER 35 U.S.C. 102/103 CAN BE MADE WHEN THE PRIOR ART PRODUCT SEEMS TO BE IDENTICAL EXCEPT THAT THE PRIOR ART IS SILENT AS TO AN INHERENT CHARACTERISTIC

Where applicant claims a composition in terms of a function, property or characteristic and the composition of the prior art is the same as that of the claim but the function is not explicitly disclosed by the reference, the examiner may make a rejection under both 35 U.S.C. 102 and 103, expressed as a 102/103 rejection. "There is nothing inconsistent in concurrent rejections for obviousness under 35 U.S.C. 103 and for anticipation under 35 U.S.C. 102." *In re Best*, 562 F.2d 1252, 1255 n.4, 195 USPQ 430, 433 n.4 (CCPA 1977). This same rationale should also apply to product, apparatus, and process claims claimed in terms of

function, property or characteristic. Therefore, a 35 U.S.C. 102/103 rejection is appropriate for these types of claims as well as for composition claims.

At the time the invention was made, those of ordinary skill in the art were aware that formation of a chemical linkage provides stabilization to a duplex structure. See, for example, Gao et al., who teach the use of aliphatic linkers with terminal thiol groups. When incorporated into complementary oligonucleotides which are allowed to hybridize, these thiols oxidize to form disulfides. Gao et al. further teach the incorporation of triethylene glycol groups as a replacement of a hairpin loop. Gao et al. teach that the introduction of both disulfide bridges and ethylene glycol groups increase the thermal stability of the duplex.

At the time the invention was made, it was recognized by those of ordinary skill in the art that the preferred oligonucleotides used for inhibiting gene expression are not longer than 25 nucleotides. This concept is not only supported by the working examples of Agrawal et al., but is also suggested in the prior art. Baracchini et al. teach at column 8 that antisense oligonucleotides are preferably 8 to 30 nucleotides and that it is more preferable to make antisense oligonucleotides that are 12 to 25 nucleotides in length. The teachings of Bennett et al. parallel those of Baracchini et al., teaching at column 7 that while antisense oligonucleotides can be up to 50 nucleotides in length, the most preferred length is 12-25 nucleotides.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to make the self-stabilized oligonucleotides of Agrawal et al. with the hybridizing region and the complementary region of equal length wherein a non-

nucleotide linker joins these two regions and use these oligonucleotides to inhibit gene expression in a mammalian cell because Agrawal et al. explicitly suggest such embodiments. One of ordinary skill in the art would find it obvious to make the oligonucleotides of Agrawal et al. wherein a linker that forms a disulfide bridge is substituted for the ethylene glycol linker specifically suggested by Agrawal et al. One of ordinary skill would have reason to do so because they would recognize these two moieties to be functional equivalents as demonstrated by Gao et al., who teach that each of these non-nucleotide linkers provide stabilization to duplexes containing them.

Because those of ordinary skill recognize based on the teachings of Baracchini et al. and Bennett et al. that antisense oligonucleotides are preferably 12-25 nucleotides in length, the person of ordinary skill in the art would further find it obvious to make and use oligonucleotides having these features of each length that falls within this limited genus, including one that is 21 nucleotides. One would expect reasonable success in making and using such oligonucleotides because Agrawal et al., Baracchini et al. and Bennett et al. each teach how to make and use oligonucleotides having these structural features.

Thus, the invention of claims 16-29 would have been obvious, as a whole, at the time the invention was made.

Claims 16-29 are rejected under 35 U.S.C. 103(a) as being unpatentable over Crooke (US 6,107,094, cited on IDS of 1/22/08), Baracchini et al. (US 5,801,154), Bennett et al. (US 5,703,054), and Gao et al. (Nucleic Acids Research 1995).

The claims are directed to a dsRNA that is 21 nucleotides in length wherein the separate strands are chemically linked with a disulfide bridge, wherein the degradation of an RNA transcript is by dsRNA-mediated interference, wherein the dsRNA mediated interference occurs due to enzymes induced by the dsRNA.

Crooke teaches at column 12 oligomeric compounds that bind to a target RNA strand and are substrates for dsRNase enzymes. The oligomeric compounds include oligoribonucleotides and other oligomeric compounds having a linear sequence of linked ribonucleoside subunits incorporated therein. The oligoribonucleotides are assembled from a plurality of nucleoside subunits. In certain preferred embodiments at least one of the nucleoside subunits bears a substituent group that increases the binding affinity of the oligoribonucleotide for a complementary strand of nucleic acid. Additionally, at least some of the nucleoside subunits comprise 2'-hydroxyl-pentofuranosyl sugar moieties. In certain embodiments of the invention, specific nucleoside subunits or internucleoside linkages are functionalized or selected to increase the nuclease resistance of the oligoribonucleotide or oligoribonucleoside. At column 5, Crooke teaches that oligomeric compounds can include 2'-substituent groups; preferred 2'-substituents include methoxy, aminoalkoxy, such as aminopropoxy. At column 14 Crooke teaches that the oligomeric compounds of the invention are preferably 15-25 nucleotides in length. One embodiment of oligomeric compounds

specifically taught by Crooke in examples 24 and 27a are artificial substrates for dsRNAse enzymes. These substrates comprise sense and antisense strands wherein one or both strands is chemically modified. Crooke exemplifies embodiments where the artificial substrate is 17 and 20 nucleotides in length.

Crooke does not explicitly embody an artificial substrate that is 21 nucleotides in length, but based on his explicit exemplification of a 20 nucleotide substrate and the teaching that preferred compounds are 15-25 nucleotides in length, the person of ordinary skill in the art would find it obvious to make artificial nuclease substrates of each length that falls within this limited genus, including one that is 21 nucleotides. Based on the disclosure of Crooke that his oligomeric compounds could be unmodified or comprise a variety of chemical modifications and the explicit teachings of artificial substrates that contain modified and unmodified nucleotides, the person of ordinary skill in the art would find it further obvious to make any of these substrates, including the 21 nucleotide substrate, with at least one chemical modification. Although Crooke does not explicitly teach that these artificial nuclease substrates specifically inhibit expression of a mammalian target gene, because these substrates meet the structural limitations of the claims, they are expected in the absence of evidence to the contrary to have this effect.

Crooke et al. do not specifically teach the dsRNA inhibits expression using dsRNA-mediated interference or that the interference occurs via an enzyme induced by the dsRNA. Because the dsRNA is substantially identical to the claimed dsRNA, the dsRNA inherently posses the functional characteristics of the claimed dsRNA, namely

inhibitions of expression of a mammalian target using dsRNA-mediated interference wherein the interference occurs via an enzyme induced by the dsRNA.

The MPEP states:

A REFERENCE TEACHING PRODUCT APPEARING TO BE SUBSTANTIALLY IDENTICAL IS MADE THE BASIS OF A REJECTION, AND THE EXAMINER PRESENTS EVIDENCE OR REASONING TENDING TO SHOW INHERENCY, THE BURDEN SHIFTS TO THE APPLICANT TO SHOW AN UNOBVIOUS DIFFERENCE

"[T]he PTO can require an applicant to prove that the prior art products do not necessarily or inherently possess the characteristics of his [or her] claimed product. Whether the rejection is based on inherency' under 35 U.S.C. 102, on prima facie obviousness' under 35 U.S.C. 103, jointly or alternatively, the burden of proof is the same...[footnote omitted]." The burden of proof is similar to that required with respect to product-by-process claims. *In re Fitzgerald,* 619 F.2d 67, 70, 205 USPQ 594, 596 (CCPA 1980) (quoting *In re Best,* 562 F.2d 1252, 1255, 195 USPQ 430, 433-34 (CCPA 1977)).

MPEP 2112.01:

PRODUCT AND APPARATUS CLAIMS WHEN THE STRUCTURE RECITED IN THE REFERENCE IS SUBSTANTIALLY IDENTICAL TO THAT OF THE CLAIMS, CLAIMED PROPERTIES OR FUNCTIONS ARE PRESUMED TO BE INHERENT

Where the claimed and prior art products are identical or substantially identical in structure or composition, or are produced by identical or substantially identical processes, a prima facie case of either anticipation or obviousness has been established. In re Best, 562 F.2d 1252, 1255, 195 USPQ 430, 433 (CCPA 1977). When the PTO shows a sound basis for believing that the products of the applicant and the prior art are the same, the applicant has the burden of showing that they are not. *In re Spada*, 911 F.2d 705, 709, 15 USPQ2d 1655, 1658 (Fed. Cir. 1990). Therefore, the prima facie case can be rebutted by evidence showing that the prior art products do not necessarily possess the characteristics of the claimed product. *In re Best*, 562 F.2d at 1255, 195 USPQ at 433.

A REJECTION UNDER 35 U.S.C. 102/103 CAN BE MADE WHEN THE PRIOR ART PRODUCT SEEMS TO BE IDENTICAL EXCEPT THAT THE PRIOR ART IS SILENT AS TO AN INHERENT CHARACTERISTIC

Where applicant claims a composition in terms of a function, property or characteristic and the composition of the prior art is the same as that of the claim but the function is not explicitly disclosed by the reference, the examiner may make a rejection under both 35 U.S.C. 102 and 103, expressed as a 102/103 rejection. "There is nothing inconsistent in concurrent rejections for obviousness under 35 U.S.C. 103 and for anticipation under 35 U.S.C. 102." *In re Best*, 562 F.2d 1252, 1255 n.4, 195 USPQ 430, 433 n.4 (CCPA 1977). This same rationale should also apply to product, apparatus, and process claims claimed in terms of function, property or characteristic. Therefore, a 35 U.S.C. 102/103 rejection is appropriate for these types of claims as well as for composition claims.

At the time the invention was made, those of ordinary skill in the art were aware that formation of a chemical linkage provides stabilization to a duplex structure. See, for example, Gao et al., who teach the use of aliphatic linkers with terminal thiol groups. When incorporated into complementary oligonucleotides which are allowed to hybridize, these thiols oxidize to form disulfides. Gao et al. further teach the incorporation of triethylene glycol groups as a replacement of a hairpin loop. Gao et al. teach that the introduction of both disulfide bridges and ethylene glycol groups increase the thermal stability of the duplex.

At the time the invention was made, it was recognized by those of ordinary skill in the art that the preferred oligonucleotides used for inhibiting gene expression are not longer than 25 nucleotides. This concept is not only supported by the working examples of Agrawal et al., but is also suggested in the prior art. Baracchini et al. teach at column 8 that antisense oligonucleotides are preferably 8 to 30 nucleotides and that it is more preferable to make antisense oligonucleotides that are 12 to 25 nucleotides in length. The teachings of Bennett et al. parallel those of Baracchini et al., teaching at column 7 that while antisense oligonucleotides can be up to 50 nucleotides in length, the most preferred length is 12-25 nucleotides.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to make the dsRNA of Crooke et al. with the hybridizing region and the complementary region of equal length wherein a non-nucleotide linker joins these two regions and use these oligonucleotides to inhibit gene expression in a mammalian cell because Agrawal et al. explicitly suggest such embodiments.

Because those of ordinary skill recognize based on the teachings of Baracchini et al. and Bennett et al. that antisense oligonucleotides are preferably 12-25 nucleotides in length, the person of ordinary skill in the art would further find it obvious to make and use oligonucleotides having these features of each length that falls within this limited genus, including one that is 21 nucleotides. One would expect reasonable success in making and using such oligonucleotides because Crooke et al., Baracchini et al. and Bennett et al. each teach how to make and use oligonucleotides having these structural features.

Thus, the invention of claims 16-29 would have been obvious, as a whole, at the time the invention was made.

Claim Rejections - 35 USC § 102 and 103 - maintained

The rejections of claims 4 and 6-9 under 35 U.S.C. 102(b) as being anticipated by Elbashir et al. (Nature 2001, of record) Tuschl et al. (WO 02/44321, of record) are withdrawn.

The rejection of claims 4 and 6-9 under 35 U.S.C. 102(b) as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over Crooke (US 6,107,094, of record) is withdrawn.

The rejection of claims 16-18 under 35 U.S.C. 103(a) as being unpatentable over Agrawal et al. (WO 94/01550, of record) is withdrawn in view of the new grounds of rejection above.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Kimberly Chong whose telephone number is 571-272-3111. The examiner can normally be reached Monday thru Friday between 7-4 pm.

If attempts to reach the examiner by telephone are unsuccessful please contact Christopher Low at 571-272-0951. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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Art Unit 1635